SAPIENZA
UNIVERSITÀ DI ROMA

rAAV2/9 – *NEU1* gene therapy in Type II of Sialidosis mouse model

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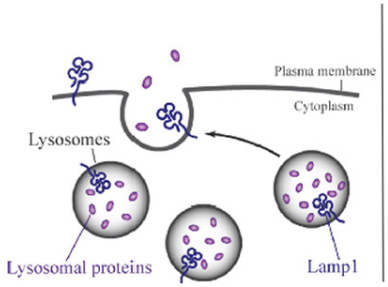
2019/2020

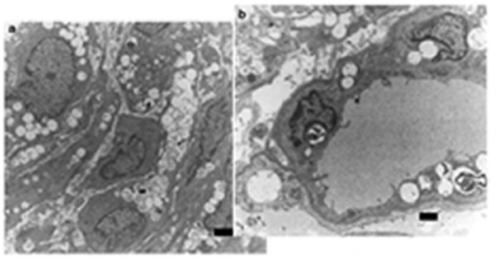
Sialidosis

- Lysosomal Storage disease
- Autosomal recessive mutations of NEU1 gene
- Affects 1 in 4.200.000 live births
- Death for renal and cardiac failure (**systemic failure**) in **severe type II sialidosis**
- Main phenotype of type II: edema and visceromegaly

Sialidosis Type II: a systemic disease

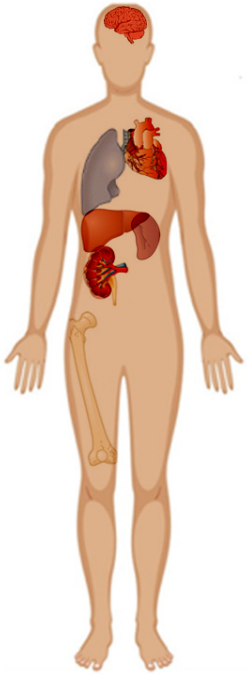
Primary affected cells:
reticulo - endothelial cells



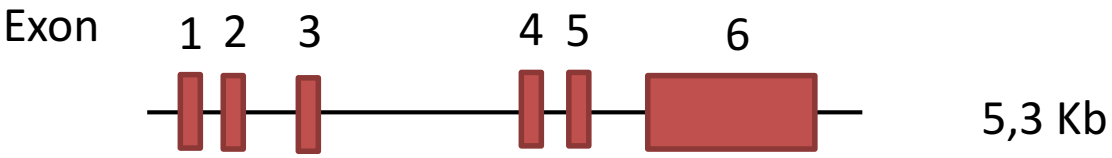


Cellular vacuolation

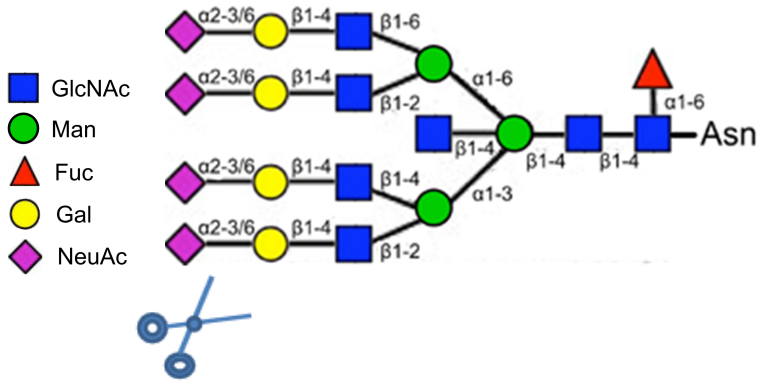
Systemic disease



NEU1 gene



encodes **neuraminidase** or **sialyase**



hydrolysis of α-**(2->3)**-, α-**(2->6)**- glycosidic linkages of **terminal sialic acid residues** in
oligosaccharides
glycoproteins
glycolipids

40 causative mutations

Aim of the work

Recovery of enzymatic function of neuraminidase 1 in CDH5-targeted tissues in Neu-/- mouse model

Work outline

Material and methods

Delivery system

Espression promoter

Animal model: Neu1 -/-

In vitro experiments

In vivo experiments

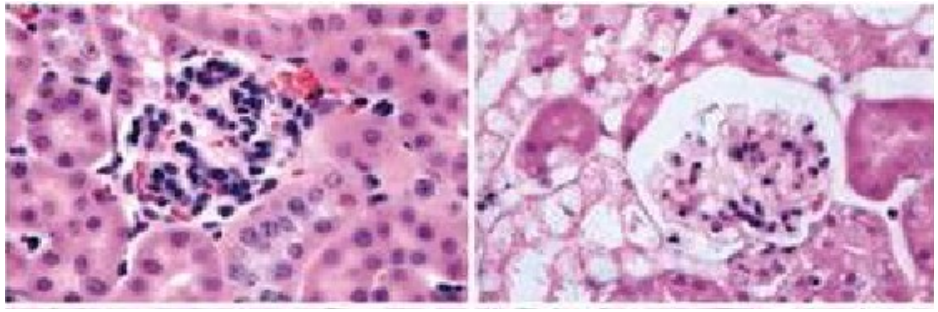
Pitfalls and solutions

Timeline and costs

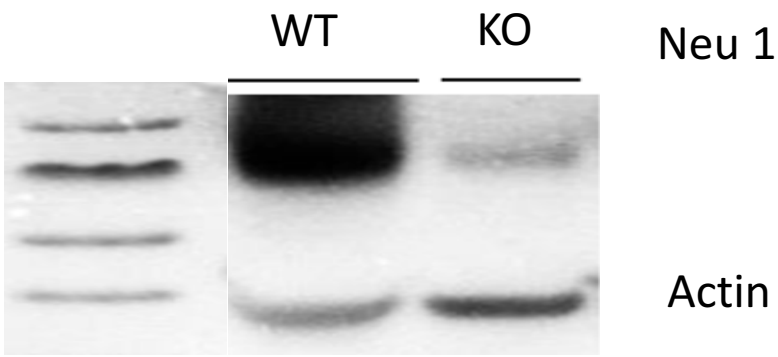
Neu 1-/- Mouse model

WT Neu 1 KO

4 weeks Kidney vacuolation

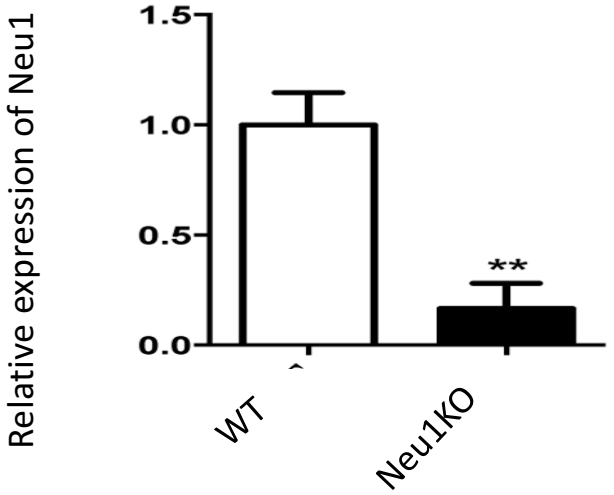


20 weeks curvature of cervical spine

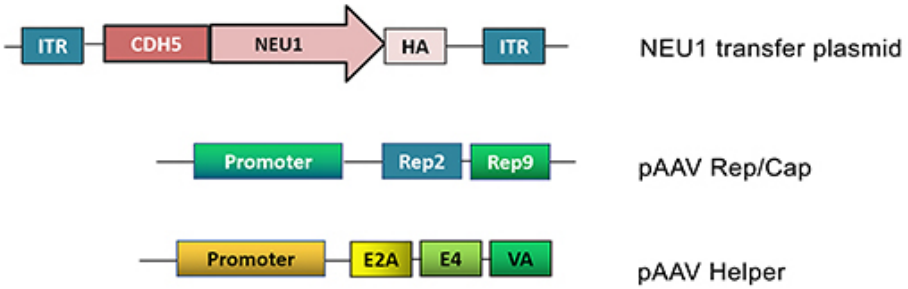


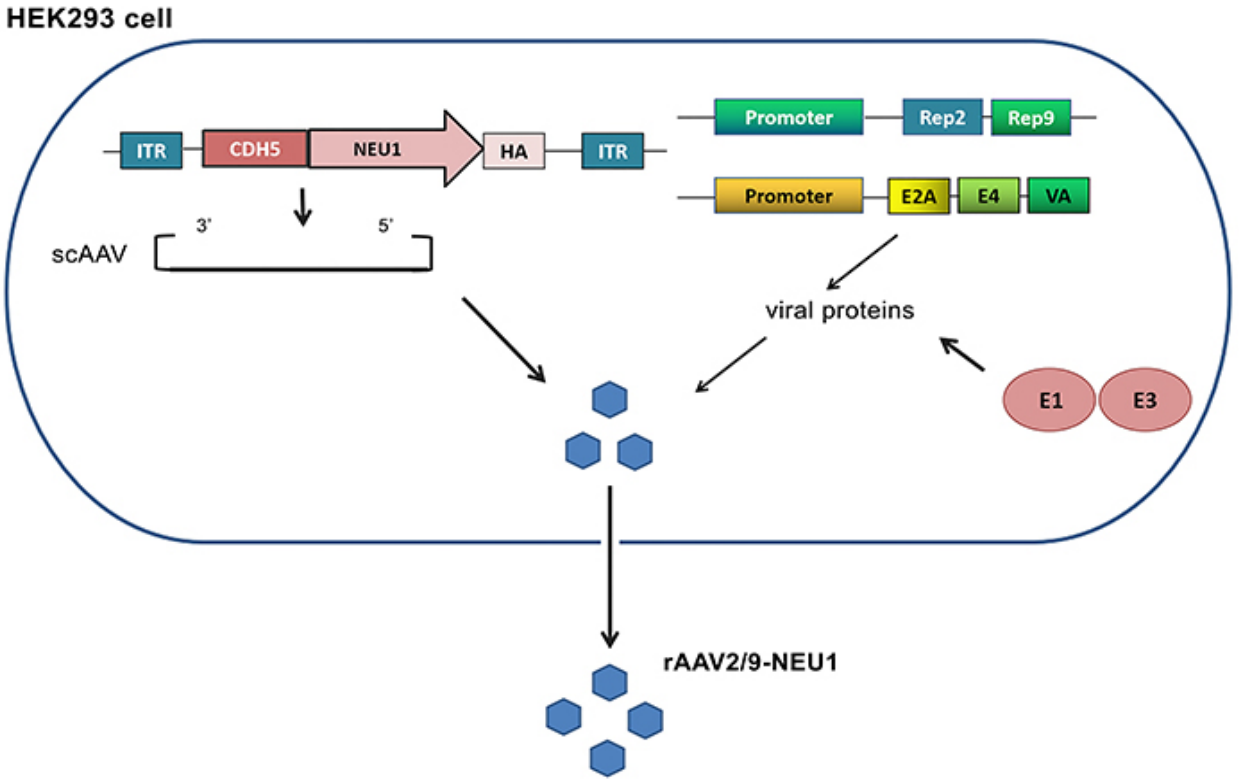
De Geest, et al., 2002

WT Neu 1 KO



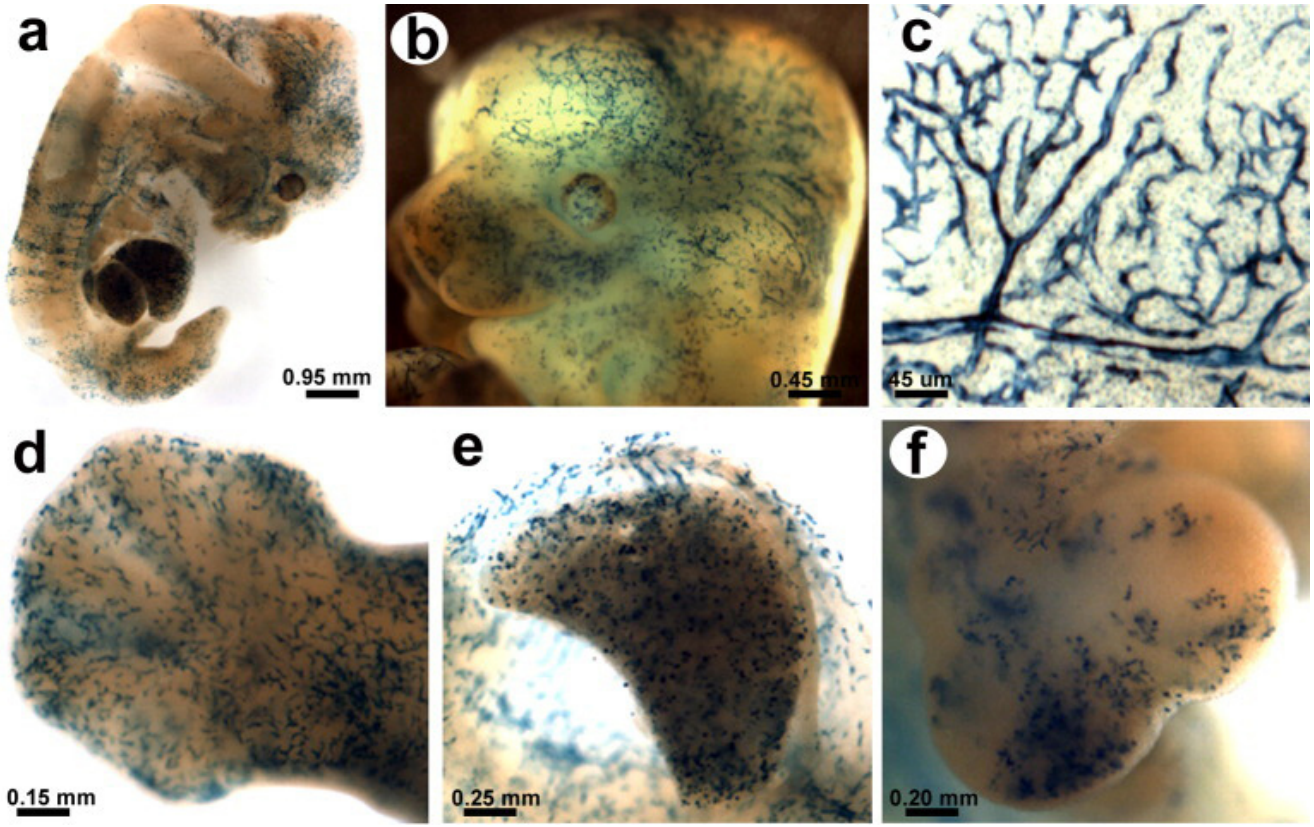
Delivery system production





Why Cdh5 promoter?

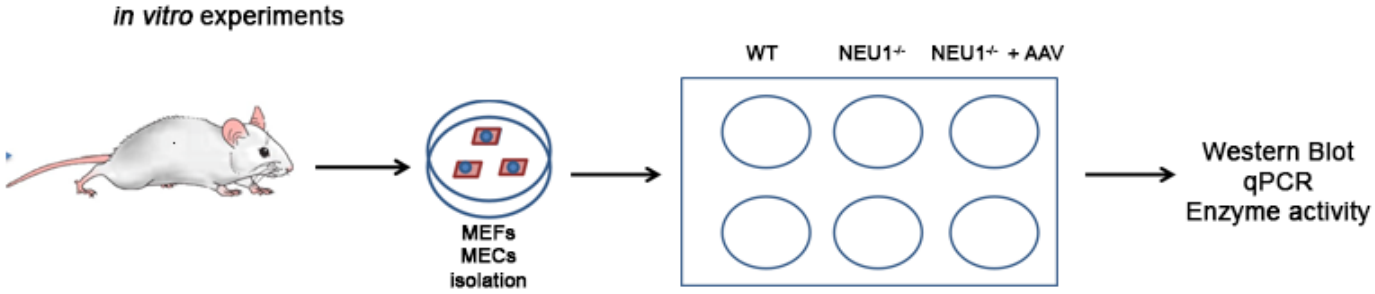
If a transgene is under VE chaderin promoter is strongly expressed in the **vasculature** of most organs : lung, heart, gut, kidney, and limb buds

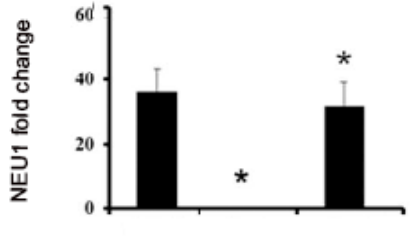


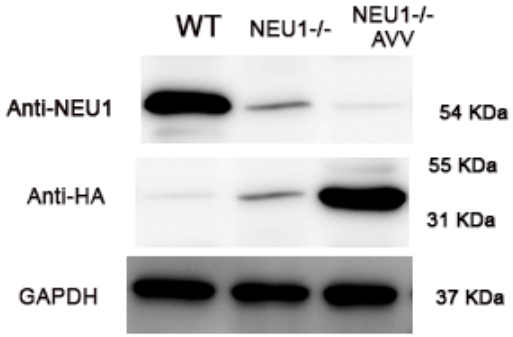
(a)Whole-mount β-Gal staining of head (b), yolk sac (c), upper limb (d), liver (e),and heart (f).

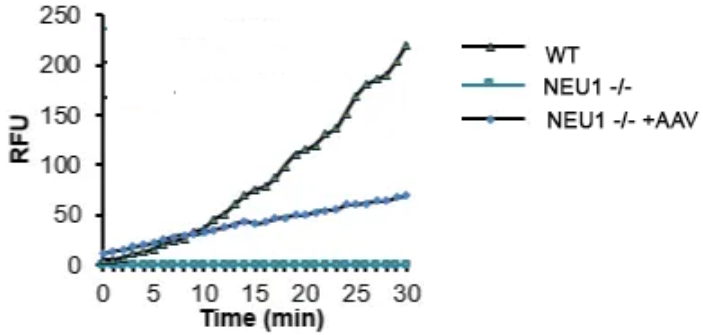
Monvoisin et al., 2006

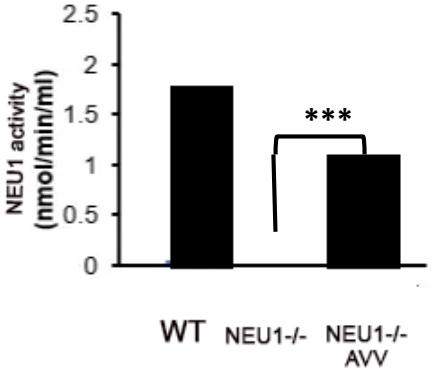
Does Cdh5-NEU1 AVV2/9 rescue the neuraminidase activity *in vitro*?



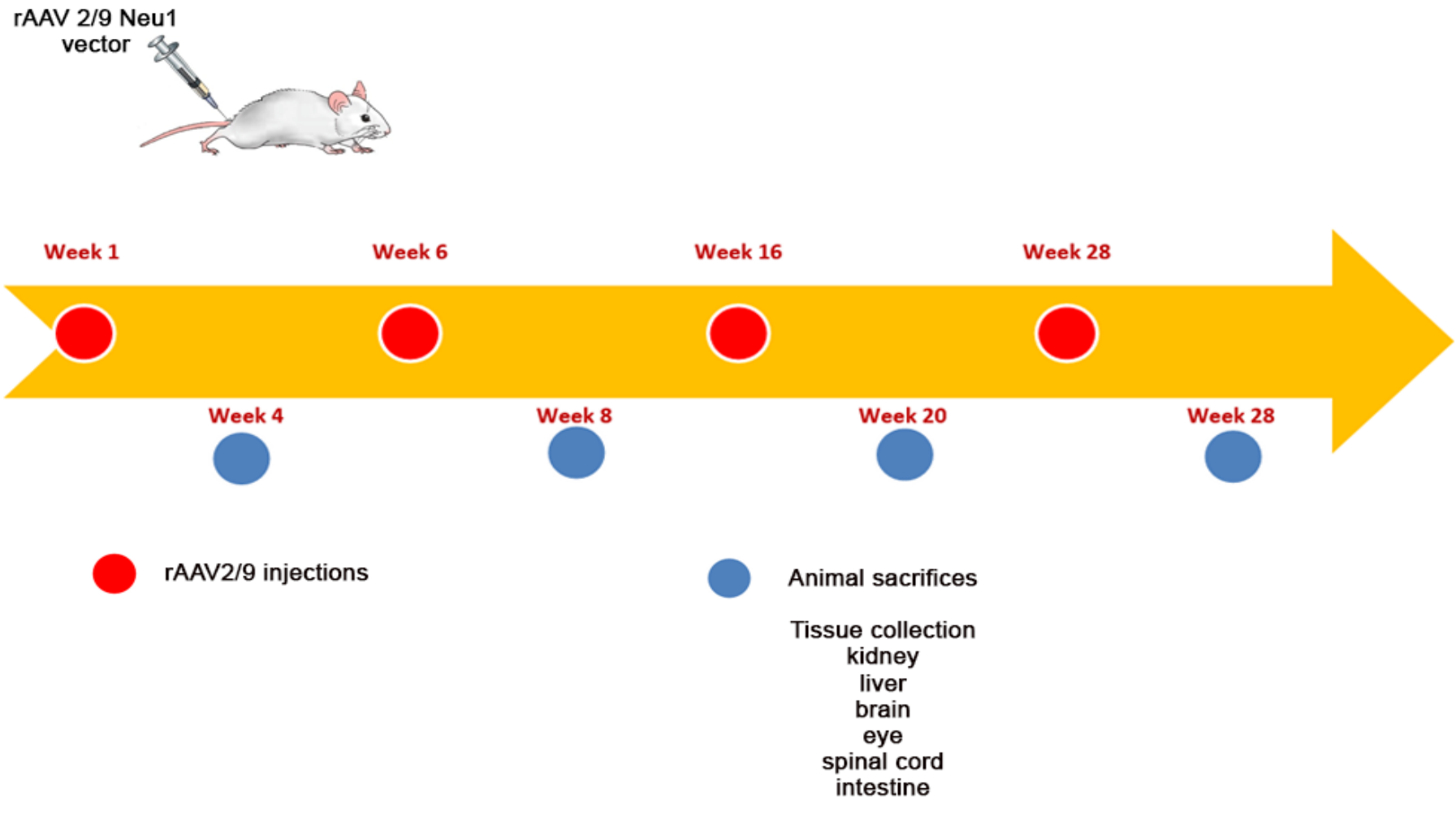




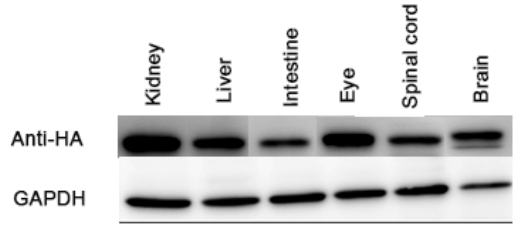


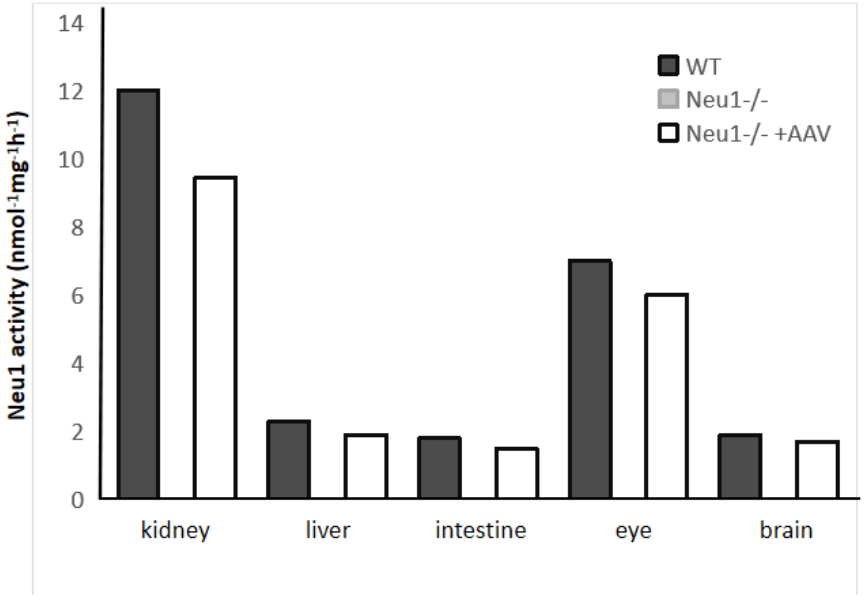


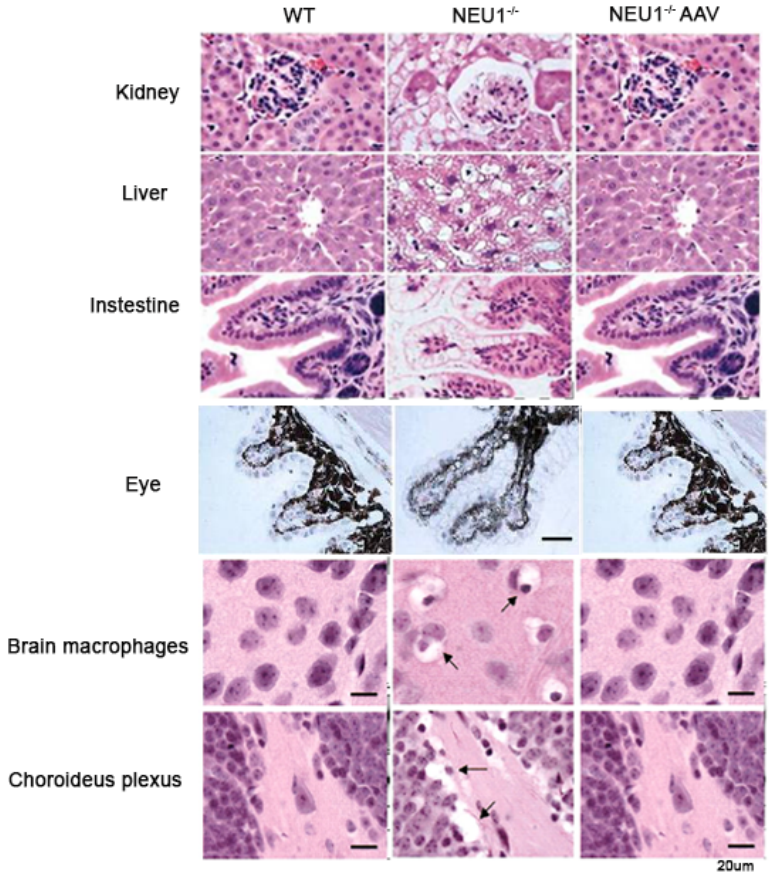
In vivo experiments



Does Cdh5-NEU1 AVV2/9 rescue the neuraminidase activity *in vivo*?







Adapted from De Geest et al., 2002

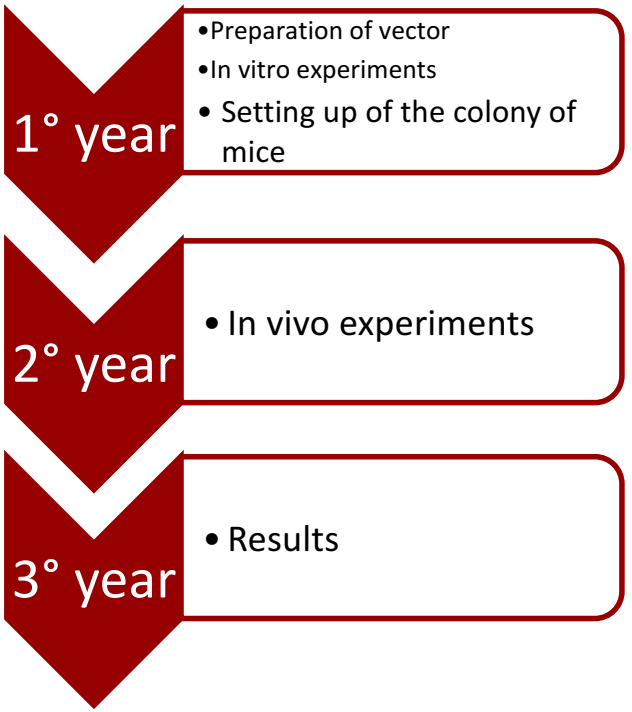
Pitfalls and solutions

Different dose required :
Correction of dose-response curves

Low NEU1 systemic expression:

Alternative promoter for NEU1 expression to target other tissues (Liver, monocytes-macrophages)

Timeline and Costs



References:

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